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Regulatory Affairs

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August 26, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 99D-0529
"Draft Guidance for Industry - Changes to an Approved NDA or ANDA"

Dear Sir or Madam:

Reference is made to the draft guidance cited above and to the Federal Register publication on June 28, 1999 announcing its availability for comments. Medeva hereby submits the following comments on the draft guidance.

1) In section III, lines 88 - 89, it is stated that "The applicant must list all changes included in the supplement or annual report in the cover letter (21 CFR 314.70(a)(6))." Listing all changes in the cover letter, if taken literally, could make the cover letter unnecessarily long and complex. This may be especially true for annual reports, where, in an effort to keep the NDA current, it is common practice to submit manufacturing and controls documents that have been updated with insubstantial changes that would not be necessarily considered annual reportable changes. Please clarify the level of detail intended for the cover letter.

2) In section VIII, SPECIFICATIONS, example C.1.a, lines 538-539, "any changes in a regulatory analytical procedure other than those identified as major changes" require submission of a supplement - changes being effected in 30 days. Any change in a regulatory analytical procedure thus needs to be reported in a supplement. This seems inconsistent with example D.2, lines 572-576, which allows the addition or revision of an alternative analytical procedure to be reported in an annual report as long as it provides the same or greater level of assurance of the identity, strength, quality, purity or potency of the material being tested as the regulatory analytical procedure. For consistency, there should be a provision to report minor changes to a regulatory analytical procedure in an annual report.

3) In section IX, PACKAGE, lines 666-667, 686-689, 698-700 and 704-706, it is stated in essence that changes in primary packaging component materials may be reported in an annual report provided the new material has been used in, and been in contact with, CDER-approved

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products of the same type. However, the specific composition of packaging components in CDER-approved products other than the general material type (e.g., HDPE) is not published or readily available. Thus, for example, a manufacturer who intends to switch to a new packaging material would be required to determine whether that new material has already been approved by CDER for use by other manufacturers for the same dosage form. As stated previously this information is not readily available and therefore should not be required.

4) On lines 612-614, it is stated "For liquid...and semisolid...dosage forms, a change to or in polymeric materials (e.g., plastic, rubber) of primary packaging components...". In regards to the phrase "in polymeric materials", while it is likely that this is meant to include a change from one polymeric material to another (e.g., HDPE to polypropylene), it should be clarified if this is also intended to include changes within a polymeric material (e.g., from one HDPE resin to another HDPE resin). Additionally, it is not clear from the examples given how to report a change in a plastic component of liquid dosage forms when changing to another plastic of the same type.

5) Example B.1 (lines 612-616) appears to conflict with Example D.4 (lines 683-694). Under example B.1, a new polymeric material that "has never been approved by CDER for use with that particular liquid dosage form" (taken to mean particular drug product) would need to be reported in a prior approval supplement. However, under example D.4, changing to a plastic screw cap, or adding a cap liner, which could be new polymeric materials never approved for use with that particular drug product can be reported in the annual report. Thus, it is not possible to determine if the Agency intends for a change to a new polymeric material that has not been previously approved for a particular drug product to be reported in a prior approval supplement or in an annual report.

6) In regards to the definition of "primary" and "secondary packaging component" (lines 846-847 and 863-864, respectively), it is not clear if a cap would be considered a primary or secondary packaging component in instances where it contains a liner. While the liner is in direct contact with the dosage form, the cap is not. Understanding that the liner would thus be considered a primary component, please clarify whether the cap is considered a primary or secondary component.

If there are any questions on these comments, or if further information is desired, please contact the undersigned by telephone at 716 274-5716, or by fax at 716 272-3952.

Sincerely,

Donald J. Handley
Manager, Regulatory Affairs

Submitted in duplicate

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